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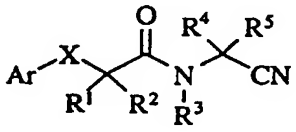
(54) Title: ACETAMIDO ACETONITRILE DERIVATIVES AS INHIBITORS OF CATHEPSIN L AND/OR CATHEPSIN S

(57) Abstract

A compound of formula (I) wherein Ar, R^1, R^2, R^3, R^4 and R^5 are defined; a composition comprising a compound of formula (I) and a carrier or diluent; a compound of formula (I) for use as a medicament, the use of a compound of formula (I) in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warn blooded animal; the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal; and a method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I).



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ACETAMIDO ACETONITRILE DERIVATIVES AS INHIBITORS OF CATHEPSIN L AND/OR CATHEPSIN S

The present invention relates to compounds that are cysteine protease inhibitors and in particular compounds that are Cathepsin L inhibitors and or Cathepsin S inhibitors especially Cathepsin S inhibitors. The invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents, to pharmaceutical compositions containing them and to a method of treating a Cathepsin L or Cathepsin S mediated disease state.

Cysteine proteases are enzymes important in normal cell physiology, but they are also associated with several disease states including inflammation, metastasis, tissue damage following myocardial infarction, bone resorption and muscle wasting in dystrophic diseases.

Cathepsins B, H, K, L, N and S are cysteinyl proteases involved in normal protein degradation and are normally located in the lysosomes of cells. However, when these enzymes are found outside the lysosomes they have been implicated as playing a causative role in a number of disease states including bone resorption disease such as osteoporosis.

The number of people living to an old age has increased dramatically in recent years. This has been marked by an increase in the number of people having osteoporosis and other diseases associated with old age. Osteoporosis is accompanied by a high incidence of bone fracture resulting in many aged patients being confined to their beds. There is therefore a great need for a pharmaceutical composition to treat or prevent this disease.

Living bone is continuously being remodelled and replenished by the process of resorption and deposition of the protein matrix and calcium minerals. These events are facilitated by the osteoclast, which has the ability to degrade and demineralise the bone, and the osteoblast which is responsible for new bone generation. In normal situations these processes are intimately linked resulting in little alteration of bone mass. However, pathological conditions exist in which there is an imbalance between their activities resulting in increased degradation and demineralisation of bone and the development of fragile and/or brittle bone structure, as seen during osteoporosis. While the exact mechanism for this resorption is not known, increased osteoclast activity, as realised by increased proteolytic activity, is a contributing factor, and selective inhibition of proteolytic action may result in the arrest or reversal of bone loss. The lysosomal cysteine proteinases, Cathepsins B, H, K, L, N

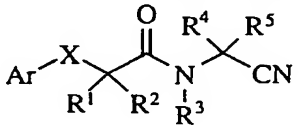
and S have been postulated as the proteinases that are responsible for osteoclast bone resorption, because of their ability to degrade insoluble type I collagens at low pH.

Cathepsins B, H, K, L, N and S have been further implicated as playing a causative role in other diseases such as rheumatoid arthritis, osteoarthritis, tumour metastasis, pneumocystitis, Crithidia fusiculata, malaria, trypanosoma brucei brucei, schistosomiasis, periodontal disease, metachromatic leukodystrophy and muscular dystrophy. Cathepsins B, H, K, L, N and S, either alone or together, have also been implicated as playing a causative role in chronic obstructive pulmonary disease (COPD).

In recent years a number of synthetic inhibitors of cysteine proteases have been disclosed. US 5,055,451 discloses a series of peptidyl methyl ketones as thiol protease inhibitors; WO 95/15749 discloses peptidyl ketones with heterocyclic leaving groups as cysteine protease inhibitors; the *in vivo* inhibition of Cathepsin B by peptidyl (acyloxy) methyl ketones was discussed in *J. Med. Chem.* **1994**, *37*, 1833-40 and these types of compounds as inhibitors of cysteine protease inhibitors were also discussed in *J. Am. Chem. Soc.*, **1988**, *110*, 4429-4431; peptidyl diazomethyl ketones as specific inactivators of thiol proteinases was discussed in *J. Biol. Chem.*, **1981**, *256*, 4, 1923-8 and in *Methods in Enzymology*, **1981**, *80*, 820-5; the inhibiting activities of 1-peptidyl-2-haloacetyl hydrazines towards Cathepsin B and calpains was discussed in *Eur. J. Med. Chem.*, **1993**, 28 297-311 and peptidyl fluoromethyl ketones as inhibitors of Cathepsin B and the implication for treatment of Rheumatoid arthritis was discussed in *Biochemical Pharmacology*, **1992**, *44*, 6, 1201-7. Thus, there is a great need for a specific cysteine protease inhibitor especially a Cathepsin L inhibitor or a Cathepsin S inhibitor.

The present invention discloses compounds with inhibitory activity of cysteine proteases and in particular of Cathepsin L and or Cathepsin S. The compounds of the invention are also useful in the treatment of chronic obstructive pulmonary disease (COPD).

Accordingly the present invention provides a compound of formula (I):



(I)

wherein

Ar is optionally substituted phenyl, optionally substituted naphthyl, Het, C_{3-12} cycloalkyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^6S-, $R^6C(O)$- and R^6CH_2- wherein $\mathbf{R^6}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; with the proviso that when Ar is a nitrogen linked Het, X is not $-N(R^7)-$ or $-O-$;

X is $-N(R^7)-$, $-S(O)_n-$, $-O-$, $-SO_2N(R^7)-$ wherein **n** = 0-2, $\mathbf{R^7}$ is H, C_{1-6}alkyl (optionally substituted with one or more of cyano, Het and R^{10}) or R^7 is C_{2-6}alkenyl (optionally substituted with R^{10}), formyl and $\mathbf{R^{10}}$ is an optionally substituted five or six membered heteroaryl ring, optionally substituted phenyl or optionally substituted naphthyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkoxy;

$\mathbf{R^1}$ is H, C_{1-6}alkyl (optionally substituted with R^8), C1-6 alkylsulphanyl (optionally substituted with R^8), C_{2-6}alkenyl, R^8, R^8S- wherein $\mathbf{R^8}$ is phenyl, C_{3-12} cycloalkyl, Het or a 5- or 6- membered heteroaryl ring, all of which are optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl,

N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and benzyloxy, with the proviso that if R^1 is C_{1-6} alkylsulphanyl (optionally substituted with R^8) or R^8S- then X is $-SO_2N(R^7)$-;

R^2 is H or C_{1-6}alkyl;

R^3 is H or C_{1-6}alkyl;

R^4 is H, C_{1-6}alkyl (optionally substituted with one or more of hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^9, R^9C_{1-6}alkylsulphanyl, R^9C_{1-6}alkylsulphinyl and R^9C_{1-6}alkylsulphonyl), or R^4 is C_{1-6}alkoxy (optionally substituted with one or more of C_{2-6}alkenyl, C_{2-6}alkynyl, R^9, R^9C_{2-6}alkenyl, R^9C_{2-6}alkynyl, Het and trifluoromethyl), or R^4 is C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^9-, R^9S-, R^9C_{1-6}alkylsulphanyl, *N*-(R^9C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl wherein **R^9** is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; and

R^5 is H or C_{1-6}alkyl; **Het** is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms;

provided that: when R^1 is H or C_{1-6} alkyl, X is O or S, and R^2 and R^3 are both hydrogen, then Ar is not pyrimid-4-yl; when R^1 and R^2 are both hydrogen, R^3 is C_{1-6} alkyl, X is O, R^4 is hydrogen, C_{1-6} alkyl, phenyl or benzyl, and R^5 is hydrogen or C_{1-4} alkyl, then Ar is not halophenyl; when R^1 and R^3 are both hydrogen, R^2 and R^5 are, independently, hydrogen or methyl, R^4 is unsubstituted pyrrolyl, thienyl or furyl, and X is O, then Ar is not 3-methyl-2,4-dichlorophenyl; when R^1 is hydrogen or C_{1-4} alkyl, R^2 is hydrogen or C_{1-4} alkyl, R^3 is hydrogen, R^4 is hydrogen, C_{1-6} alkyl or phenyl, and X is O, S, NH or N(C_{1-4} alkyl), then Ar is not phenyl optionally substituted with: halo, C_{1-4} alkyl, CF_3, C_{1-4} alkoxy, CO_2H, CO_2(C_{1-4} alkyl), $CONH_2$, NO_2, CN, $CH_2N(CH_3)_2$, S(C_{1-4} alkyl) or mono- or di-chlorobenzyl; when R^1,

R^2, R^3 and R^5 are all hydrogen, R^4 is $SO_2CH_2CH_3$, and X is SO_2, then Ar is not phenyl; and, when R^1, R^2, R^3, R^4 and R^5 are all hydrogen, and X is SO_2NH, then Ar is not 4-methylphenyl; or a pharmaceutically acceptable salt thereof.

In this specification the term 'alkyl' includes straight chained and branched structures and ring systems. For example, C_{1-6}alkyl includes propyl, isopropyl, *t*-butyl, cyclopropyl and cyclohexyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only, references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only and references to individual cycloalkyl groups such as cyclohexyl are specific to the cyclic groups only.

A similar convention applies to other radicals, for example "aminoC_{1-6}alkyl" includes 1-aminoethyl and 2-aminoethyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

"Het" means, unless otherwise further specified, a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms. Examples of heteroatoms include nitrogen, oxygen and sulphur. Examples of "Het" include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl. Further examples of "Het" include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, thiomorpholino and morpholino. Preferably "Het" is morpholino.

"5- or 6- membered heteroaryl ring" means, unless otherwise further specified, a 5- or 6- membered ring that contains some degree of unsaturation, with up to four ring heteroatoms selected from nitrogen, oxygen and sulphur. Examples of "5- or 6- membered heteroaryl ring" include thienyl, furyl, imidazolyl, thiazolyl, pyrimidinyl, pyridinyl, pyrrolyl and pyrazolyl. Examples of "5- membered heteroaryl ring" include thienyl, furyl, imidazolyl, thiazolyl and pyrrolyl.

Examples of "C_{1-6}alkanoyloxy" are acetoxy and propionyloxy. Examples of "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkylsulphanyl" include methylthio and ethylthio. Examples of "C_{1-6}alkylsulphinyl" include methylsulphinyl and ethylsulphinyl. Examples of "C_{1-6}alkylsulphonyl" include mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" include acetyl and propionyl. Examples of "C_{1-6}alkylamino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino"

include *N,N*-dimethylamino, *N,N*-diethylamino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl" are 2-*N*-methylaminoethyl and 3-*N*-ethylaminopropyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl" are 2-(*N,N*-dimethylamino)ethyl and 3-(*N,N*-diethylamino)propyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-methylsulphamoyl and *N*-ethylsulphamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-dimethylsulphamoyl and *N,N*-diethylsulphamoyl. Examples of "R^9C_{1-6}alkylsulphanyl" include R^9methylthio and R^9ethylthio. Examples of "R^9C_{1-6}alkylsulphinyl" include R^9methylsulphinyl and R^9ethylsulphinyl. Examples of "R^9C_{1-6}alkylsulphonyl" include R^9mesyl and R^9ethylsulphonyl. Examples of R^9C_{2-6}alkenyl are R^9vinyl and R^9allyl. Examples of "C_{2-6}alkynyl" are R^9ethynyl and R^9propyn-1-yl. Examples of "*N*-(R^9C_{1-6}alkyl)carbamoyl" are R^9methylaminocarbonyl and R^9ethylaminocarbonyl. Examples of "*N*-(HetC_{1-6}alkyl)carbamoyl" are morpholinomethylaminocarbonyl and 2-(piperidinoethyl)aminocarbonyl. Examples of "C_{3-12}cycloalkyl" are cyclopropyl, cyclopentyl and cyclohexyl.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. For example where optional substituents are chosen from one or more halo, C_{1-6}alkoxy and C_{1-6}alkyl, examples of possible combinations of substituents include 1) a bromo group, 2) two chloro groups, 3) a methoxy, ethoxy and propoxy substitutent, 4) a fluoro and a methoxy group, 5) a methoxy, a methyl and an ethyl group, and 6) a chloro, a methoxy and an ethyl group.

In one aspect the present invention provides a compound of formula (**I**), wherein **Ar** is optionally substituted phenyl, optionally substituted naphthyl, Het, C_{3-12}cycloalkyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl,

N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^6S-, $R^6C(O)$- and R^6CH_2- wherein $\mathbf{R^6}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl with the proviso that when Ar is a nitrogen linked Het, X cannot be -N(R^7)- or -O-; **X** is -N(R^7)-, -S(O)$_n$-, -O-, -SO_2N(R^7)- wherein **n** = 0-2, $\mathbf{R^7}$ is H, C_{1-6}alkyl (optionally substituted with one or more of cyano, Het and R^{10}) or R^7 is C_{2-6}alkenyl (optionally substituted with R^{10}), formyl and $\mathbf{R^{10}}$ is an optionally substituted five or six membered heteroaryl ring, optionally substituted phenyl or optionally substituted naphthyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkoxy; $\mathbf{R^1}$ is H, C_{1-6}alkyl (optionally substituted with R^8), C_{1-6}alkylsulphanyl (optionally substituted with R^8), C_{2-6}alkenyl, R^8, R^8S- wherein $\mathbf{R^8}$ is phenyl, C_{3-12}cycloalkyl, Het or an optionally substituted five or six membered heteroaryl ring which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and benzyloxy with the proviso that if R^1 is C_{1-6}alkylsulphanyl (optionally substituted with R^8) or R^8S- then X must be -SO_2N(R^7)-; $\mathbf{R^2}$ is H or C_{1-6}alkyl; $\mathbf{R^3}$ is H or C_{1-6}alkyl; $\mathbf{R^4}$ is an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy,

trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; and $\mathbf{R^5}$ is H or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof.

In a further aspect the present invention provides a compound of formula (I), wherein **Ar** is optionally substituted phenyl, optionally substituted naphthyl or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^6S-, $R^6C(O)$- and R^6CH_2- wherein $\mathbf{R^6}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

X is $-N(R^7)-$, $-S(O)_n-$, $-O-$, $-SO_2N(R^7)-$ wherein $\mathbf{n} = 0\text{-}2$, $\mathbf{R^7}$ is H, C_{1-6}alkyl (optionally substituted with one or more of cyano, Het and R^{10}) or R^7 is C_{2-6}alkenyl (optionally substituted with R^{10}), formyl and $\mathbf{R^{10}}$ is an optionally substituted five or six membered heteroaryl ring, optionally substituted phenyl or optionally substituted naphthyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkoxy;

$\mathbf{R^1}$ is H, C_{1-6}alkyl (optionally substituted with R^8), C_{2-6}alkenyl, R^8S- wherein $\mathbf{R^8}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and benzyloxy;

$\mathbf{R^2}$ is H or C_{1-6}alkyl;

$\mathbf{R^3}$ is H or C_{1-6}alkyl;

$\mathbf{R^4}$ is H, C_{1-6}alkyl (optionally substituted with one or more of hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^9, R^9C_{1-6}alkylsulphanyl, R^9C_{1-6}alkylsulphinyl and R^9C_{1-6}alkylsulphonyl), or R^4 is C_{1-6}alkoxy (optionally substituted with one or more of C_{2-6}alkenyl, C_{2-6}alkynyl, R^9, R^9C_{2-6}alkenyl, R^9C_{2-6}alkynyl, Het and trifluoromethyl), or R^4 is C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^9-, R^9S-, R^9C_{1-6}alkylsulphanyl, *N*-(R^9C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl wherein $\mathbf{R^9}$ is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; and

$\mathbf{R^5}$ is H or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

According to a further feature of the present invention there is provided a compound of formula (I) wherein:

Ar is optionally substituted phenyl, optionally substituted naphthyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino,

N,N-(C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^6S-, $R^6C(O)$- and R^6CH_2- wherein $\mathbf{R^6}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto; C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

X is $-N(R^7)-$, $-S(O)_n-$, $-O-$, $-SO_2N(R^7)-$ wherein $\mathbf{n} = 0\text{-}2$, $\mathbf{R^7}$ is H, C_{1-6}alkyl (optionally substituted with one or more of cyano, Het and R^{10}) or R^7 is C_{2-6}alkenyl (optionally substituted with R^{10}), formyl and $\mathbf{R^{10}}$ is an optionally substituted five or six membered heteroaryl ring, optionally substituted phenyl or optionally substituted naphthyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkoxy;

$\mathbf{R^1}$ is H, C_{1-6}alkyl (optionally substituted with R^8), C_{2-6}alkenyl, R^8S- wherein $\mathbf{R^8}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and benzyloxy;

$\mathbf{R^2}$ is H or C_{1-6}alkyl;

$\mathbf{R^3}$ is H or C_{1-6}alkyl;

$\mathbf{R^4}$ is H, C_{1-6}alkyl (optionally substituted with one or more of hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^9, R^9C_{1-6}alkylsulphanyl,

R^9C_{1-6}alkylsulphinyl and R^9C_{1-6}alkylsulphonyl), or R^4 is C_{1-6}alkoxy (optionally substituted with one or more of C_{2-6}alkenyl, C_{2-6}alkynyl, R^9, R^9C_{2-6}alkenyl, R^9C_{2-6}alkynyl, Het and trifluoromethyl), or R^4 is C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^9-, R^9S-, R^9C_{1-6}alkylsulphanyl, *N*-(R^9C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl wherein **R^9** is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; and

R^5 is H or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

Preferred values for Ar, X, R^1, R^2, R^3, R^4 and R^5 are as follows.

Preferably Ar is an optionally substituted phenyl, optionally substituted naphthyl or an optionally substituted 5 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, *N,N*-(C_{1-6}alkyl)$_2$amino and *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl.

In another aspect of the invention preferably Ar is an optionally substituted phenyl, optionally substituted naphthyl, morpholino or an optionally substituted 5 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, *N,N*-(C_{1-6}alkyl)$_2$amino and *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl with the proviso that when Ar is morpholino X cannot be -N(R^7)- or -O-. The 5-membered heteroaryl ring is, for example, thienyl, furyl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl or isothiazolyl. The 5-membered ring is suitably thienyl.

More preferably Ar is an optionally substituted phenyl, optionally substituted naphthyl and optionally substituted thienyl said optional substituents being chosen from one or more fluoro, chloro, bromo, methoxy, methyl, nitro, acetylamino, trifluoromethyl, *N,N*-dimethylamino or *N,N*-dimethylaminomethyl.

In another aspect of the invention more preferably Ar is an optionally substituted phenyl, optionally substituted naphthyl, morpholino and optionally substituted thienyl said optional substituents being chosen from one or more fluoro, chloro, bromo, methoxy, methyl, nitro, acetylamino, trifluoromethyl, *N,N*-dimethylamino or *N,N*-dimethylaminomethyl with the proviso that when Ar is morpholino X cannot be $-N(R^7)-$ or -O-.

Particularly Ar is phenyl which is optionally substituted with 1 to 3 fluoro, chloro or bromo.

In another aspect of the invention particularly Ar is morpholino or phenyl which is optionally substituted with 1 to 3 fluoro, chloro or bromo with the proviso that when Ar is morpholino X cannot be $-N(R^7)-$ or -O-.

More particularly Ar is phenyl, 2-fluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2,6-dibromophenyl and 2,4,6-trichlorophenyl.

In another aspect of the invention more particularly Ar is morpholino, phenyl, 2-fluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2,6-dibromophenyl and 2,4,6-trichlorophenyl with the proviso that when Ar is morpholino X cannot be $-N(R^7)-$ or -O-.

Preferably X is $-N(R^7)-$, $-S(O)_n-$, -O- and $-SO_2N(R^7)-$ wherein n = 0-2, R^7 is H, C_{1-6}alkyl (optionally substituted with cyano, Het or R^{10}) or R^7 is C_{2-6}alkenyl (optionally substituted with R^{10}), and R^{10} is an optionally substituted five or six membered heteroaryl ring or optionally substituted phenyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, *N,N*-$(C_{1-6}$alkyl$)_2$amino, C_{1-6}alkyl and C_{1-6}alkoxy. Het is as defined above (that is it is: a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; for example pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl or morpholinyl). When X is $-SO_2N(R^7)-$ the nitrogen atom is attached to the CR^1R^2 group and the sulphur is attached to the Ar group.

More preferably X is -N(Me)-, -S-, -SO-, $-SO_2-$, -O- and $-SO_2N(R^7)-$ wherein R^7 is hydrogen, methyl, ethyl, propyl, isobutyl, cyanoethyl, morpholinoethyl, furylmethyl, thienylmethyl, pyridylmethyl, phenylallyl or benzyl, where said phenylallyl or benzyl is optionally substituted with methoxy, nitro, chloro, trifluoromethyl, methyl or *N,N*-dimethylamino.

Particularly X is -O-, $-SO_2-$ and $-SO_2N(R^7)-$ wherein R^7 is hydrogen, furylmethyl, thienylmethyl, pyridylmethyl, phenylallyl or benzyl, where said benzyl is optionally substituted with methoxy, nitro, chloro, trifluoromethyl, methyl or *N,N*-dimethylamino.

More particularly X is -O-, $-SO_2-$ and $-SO_2N(R^7)-$ wherein R^7 is hydrogen, fur-2-ylmethyl, thien-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, phenylallyl or benzyl, where said benzyl is optionally substituted with methoxy, nitro, chloro, trifluoromethyl, methyl or *N,N*-dimethylamino.

In another aspect of the invention when **X** is $-SO_2N(R^7)-$ preferably R^7 is not hydrogen.

In another aspect of the invention when **X** is $-SO_2N(R^7)-$ preferably R^7 is optionally substituted benzyl wherein said optional substituents are as defined for R^{10} above.

Preferably R^1 is hydrogen, C_{2-6}alkenyl and C_{1-6}alkyl which is optionally substituted with phenyl where said phenyl is optionally substituted by one or more groups chosen from halo, cyano, C_{1-6}alkoxy, nitro, C_{1-6}alkylsulphonyl and benzyloxy.

More preferably R^1 is hydrogen, methyl, ethyl, propyl, isobutyl, 2-methylbut-2-ene and benzyl where said phenyl is optionally substituted with one group chosen from fluoro, chloro, methoxy, benzyloxy, mesyl, nitro and cyano.

Particularly R^1 is hydrogen and benzyl where said phenyl is optionally substituted with methoxy, fluoro, chloro, mesyl, nitro or cyano.

More particularly R^1 is hydrogen, benzyl, 2-fluorobenzyl, 3-methoxybenzyl, 3-chlorobenzyl, 3-nitrobenzyl, 4-mesylbenzyl and 4-cyanobenzyl.

In another aspect of the invention preferably R^1 is hydrogen.

Preferably R^2 is hydrogen.

Preferably R^3 is hydrogen.

Preferably R^4 is hydrogen, C_{1-6}alkyl (optionally substituted with C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl and C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with C_{2-6}alkynyl), C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkylsulphanyl, R^9- and N-(R^9C_{1-6}alkyl)carbamoyl wherein R^9 is phenyl or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl and halo. Het is as defined above (that is it is: a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring

heteroatoms; for example pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl or morpholinyl).

More preferably R^4 is hydrogen, methyl, methoxy, methoxycarbonyl, ethoxycarbonyl, methylthio, ethylthio, isopropylthio, methylthiomethyl, methylthioethyl, ethynyloxy, propynyloxy, carbamoyl, methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isobutylaminocarbonyl, furyl (optionally substituted with methyl), pyridyl, thienyl (optionally substituted with bromo or methyl), N-methylpyrrolyl, benzylaminocarbonyl, pyridylmethylaminocarbonyl and morpholinoethylaminocarbonyl.

Particularly R^4 is methoxy, isopropylthio, propynyloxy, furyl (optionally substituted with methyl) and thienyl.

More particularly R^4 is methoxy, isopropylthio, propyn-1-yloxy, fur-2-yl, 5-methylfur-2-yl and thien-2-yl.

In another aspect of the invention preferably R^4 is an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl and halo.

More preferably R^4 is optionally substituted thienyl or furyl said optional substituents being chosen from one or more of C_{1-6}alkyl and halo.

Particularly R^4 is thienyl.

More particularly R^4 is thien-2-yl.

Preferably R^5 is hydrogen or methyl.

More preferably R^5 is hydrogen.

According to another aspect of the present invention there is provided a compound of the formula (I) wherein:

Ar is an optionally substituted phenyl, optionally substituted naphthyl or an optionally substituted 5 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, *N,N*-(C_{1-6}alkyl)$_2$amino and *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl;

X is -N(R^7)-, -S(O)$_n$-, -O- or -SO_2N(R^7)- wherein n = 0-2, R^7 is H, C_{1-6}alkyl (optionally substituted with cyano, Het and R^{10}) or C_{2-6}alkenyl (optionally substituted with R^{10}), and R^{10} is an optionally substituted five or six membered heteroaryl ring or optionally substituted phenyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl or C_{1-6}alkoxy;

R^1 is hydrogen, C_{2-6}alkenyl or C_{1-6}alkyl which is optionally substituted with phenyl where said phenyl is optionally substituted by one or more groups chosen from halo, cyano, C_{1-6}alkoxy, nitro, C_{1-6}alkylsulphonyl and benzyloxy;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen, C_{1-6}alkyl (optionally substituted with C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl and C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with C_{2-6}alkynyl), C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkylsulphanyl, R^9- or *N*-(R^9C_{1-6}alkyl)carbamoyl wherein R^9 is phenyl or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl or halo; and

R^5 is hydrogen or methyl;

or a pharmaceutically acceptable salt thereof.

A further preferred class of compounds is that of formula (I) wherein:

Ar is phenyl which is optionally substituted with 1 to 3 fluoro, chloro or bromo;

X is -O-, -SO_2- or -$SO_2N(R^7)$- wherein R^7 is hydrogen, furylmethyl, thienylmethyl, pyridylmethyl, phenylallyl or benzyl, where said benzyl is optionally substituted with methoxy, nitro, chloro, trifluoromethyl, methyl or *N,N*-dimethylamino;

R^1 is hydrogen or benzyl where said phenyl is optionally substituted with methoxy, fluoro, chloro, mesyl, nitro or cyano;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is methoxy, isopropylthio, propynyloxy, furyl (optionally substituted with methyl) and thienyl; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt thereof.

Preferred compounds are those of Examples 156-158 or a pharmaceutically acceptable salt thereof.

Especially preferred compounds are those of Examples 5, 19, 20, 27, 31, 38, 42, 43, 45, 46, 50, 51, 91, 92, 93, 94, 97, 98, 100, 101, 102, 104, 106, 108, 109, 111, 112, 114, 115, 116, 117, 120, 122, 126, 141, 143 or 146 or a pharmaceutically acceptable salt thereof.

Suitable pharmaceutically acceptable salts include acid addition salts such as the methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example a sodium salt, an alkaline earth metal salt for example a calcium or a magnesium salt, an organic amine salt for example a salt with triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or an amino acid for example a lysine salt. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a sodium salt.

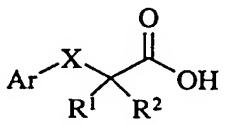
Some compounds of formula **(I)** may possess chiral centres. It is to be understood that the invention encompasses all such optical isomers and diasteroisomers of compounds of formula **(I)** which possess cysteine protease inhibitory activity.

The invention further relates to all tautomeric forms of the compounds of formula **(I)**.

It is also to be understood that certain compounds of the formula **(I)** can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt thereof. According to this aspect of the invention there is provided a process (in which variable groups are as defined for formula **(I)** unless otherwise stated) which comprises:

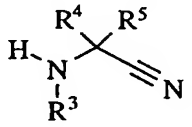
a) reacting an acid of formula **(II)**:



(II)

or a reactive derivative thereof;

with an amine of formula **(III)**:



(III)

A suitable reactive derivative of an acid of the formula (II) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate, an alcohol such as 1-hydroxybenzotriazole or a uronium salt such as 2-(1-benzotriazolyl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V); an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N,N-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

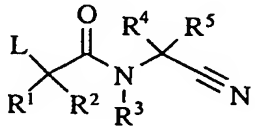
The reaction is preferably carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide or hydroxide, for example sodium carbonate or potassium carbonate, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo-[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, acetonitrile, tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide, and at a temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

b) reaction of a compound of formula (IV):

Ar-X-H

(IV)

with a compound of formula (V):



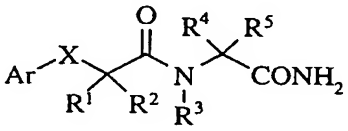
(V)

wherein L is a displaceable group.

A suitable displaceable group L is, for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

The reaction is preferably carried out in the presence of a suitable base as defined hereinbefore such as potassium carbonate. The reaction is also preferably carried out in a suitable inert solvent or diluent as defined hereinbefore such as N,N-dimethylformamide and at a temperature in the range of -0 to 100°C conveniently 25°C to 100°C.

c) dehydration of a compound of formula (**VI**):



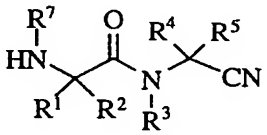
(**VI**)

under standard conditions.

For example such a dehydration reaction may conventionally be carried out by reaction with a reagent such as trifluoroacetic anhydride. The reaction can conveniently be conducted in the presence of a suitable base as defined hereinbefore such as, for example, triethylamine. The reaction is also preferably carried out in a suitable inert solvent or diluent, as defined hereinbefore such as dichloromethane and at a temperature in the range, for example, -10°C to reflux conveniently 10°C to reflux.

d) for compounds of formula (**I**) where X is $-SO_2N(R^7)-$;

reacting a compound of formula (**VII**):



(**VII**)

with a compound of formula (**VIII**):

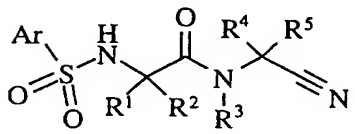
$$Ar\text{-}SO_2\text{-}L$$

(**VIII**)

where L is a displaceable group as defined above;

The reaction is conveniently performed in the presence of a base as defined hereinbefore, such as triethylamine. The reaction is also preferably carried out in a suitable inert solvent or diluent as defined hereinbefore such as tetrahydrofuran and at a temperature in the range -20 to 100°C preferably 0 to 20°C.

e) For the preparation of compounds of formula (I) where X is $-SO_2N(R^7)-$ the reaction of a compound of formula (IX):



(IX)

with a compound of formula (X):

R^7-L

(X)

wherein L is a suitable displaceable group as defined above.

The reaction can conveniently be conducted in the presence of a suitable base as defined hereinbefore such as potassium carbonate, in a suitable inert solvent or diluent as defined hereinbefore such as acetonitrile and at a temperature in the range of 25°C to reflux, conveniently 50°C to reflux.

If not commercially available, the necessary starting materials for the procedures described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, by techniques which are analogous to the above described procedures or by techniques which are analogous to the procedures described in the examples.

For example, it will be appreciated that certain of the optional substituents on a phenyl or naphthyl or a heteroaryl ring in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents.

The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and a Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by, for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an

arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel, for example, those of the formula **(VI)** and these are provided as a further feature of the invention.

According to a further feature of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

In order to use a compound of the formula **(I)** or a pharmaceutically acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in the inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

In a further aspect the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

In a still further aspect the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal, such as man.

In a still further aspect the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal, such as man.

A method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

According to a further feature of the present invention there is provided a method for producing inhibition of a cysteine protease in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

In particular the invention provides the use of a compound of the formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of Cathepsin S in a warm blooded animal, such as man.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in the inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in the inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100 mg and 1 g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 1 $mgkg^{-1}$ to 100 $mgkg^{-1}$ of the compound, preferably in the range of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Inhibition of Cathepsin L and S.

The pharmaceutically-acceptable compounds of the present invention are useful in the inhibition of Cathepsin L and Cathepsin S, having a good activity *in vitro* against human Cathepsin L, human Cathepsin S and rabbit Cathepsin L.

Cathepsin L Assay

Recombinant human Cathepsin L was cloned and expressed in E Coli and purified using the method as described by Zeneca Limited, GB 2 306 961 A (published 14.05.1997).

Rabbit Cathepsin L was purified from rabbit liver as described by Maciewicz R. A. and Etherington D. J. (Biochem. J. (1988) 256, 433-440) except the liver homogenate supernatant was concentrated by fractionation with $(NH_4)_2SO_4$ (20-80% saturation), and the pellet taken up and dialysed against 20mM NaAcetate pH 5.5, 1mM ethylenediaminetetraacetic acid (EDTA). The supernatant was then applied to a CM Sepharose ion exchange column and Cathepsin L eluted by gradient elution (0.25-0.75M NaCl). Fraction activity was determined using the synthetic substrate NCBz-Phe-Arg-NHMec as described. Cathepsin L fractions were pooled and desalted on a Sephacryl S100 column. Active fractions were pooled, adjusted to 20% saturation $(NH_4)_2SO_4$ and concentrated on a phenyl sepharose column. The remaining purification steps were as described.

Cathepsin L activity was measured based on the method of Barrett and Kirschke (1981 Methods in Enzymology, **80**, 535-561), using the fluorogenic substrates NCBz-Phe-Arg-NHMec. Inhibitors were identified by their ability to decrease the generation of the fluorescent leaving group (NHMec). Briefly the assay was as follows:

rHuman Cathepsin L or rabbit Cathepsin L (0.025 pmoles) was pre-incubated with or without test compound in 0.1M sodium acetate buffer pH4.5, 10mM cysteine, 0.1% BRIJ™ 35 at 25°C for 15 minutes in a solid black 96 well plate. Synthetic substrate, 20μM NCBz-Phe-Arg-NHMec, was added and the mixture incubated at 37°C for 30 minutes. The reaction was stopped by the addition of 0.1M sodium chloroacetate pH 4.3. Fluorescence was determined using a Fluoroskan II plate reader; excitation 355nm, emission 460nm. Compound potency was determined from the raw fluorescence data by calculating the IC_{50} against each enzyme using a PC graph drawing software package.

Cathepsin S assay.

Cloning and Expression of human Cathepsin S.

Recombinant human Cathepsin S was cloned and expressed in Baculovirus, by the following method. The cDNA sequence for human Cathepsin S is available in the EMBL database Accession Number M90696. This database sequence was used to prepare, by PCR on mRNA from human tissues, a recombinant plasmid carrying an insert with a DNA sequence identical to that of Cathepsin S in the EMBL database (Acc. no. M90696). The techniques for mRNA isolation, PCR and cloning are standard techniques known by those skilled in the art. Sequence determination of the recombinant insert was carried out using established DNA sequencing techniques.

The PCR was done so as to introduce an EcoRI cloning site 5' of the 'ATG' of Cathepsin S and an XbaI cloning site 3' of the 'Stop' codon. The PCR product was cloned between the EcoRI and XbaI sites of the baculovirus transfer vector pFASTBAC-1 (Bac-to-Bac™ Expression System commercially available from Gibco BRL –Life Technologies (cat. no. 10359-016)). This recombinant construct was used to generate, by standard techniques, a recombinant baculovirus capable of expressing preprocathepsin S.

Expression of recombinant Cathepsin S was tested for the baculoviral constructs by infection of two insect cell lines : Sf9 cells (ATCC no. CRL-1711) and T.ni cells (Invitrogen, cat. no. B855-02).

Purification of Cathepsin S

Method 1.

Procathepsin S was found in the insect cell medium and acid activated. The medium was mixed with an equal volume of 100mM Sodium Acetate buffer pH 4.5, 5mM dithiothreitol (DTT) and 5mM EDTA and incubated for one hour at 37°C method of Maubach et al (Eur. J. Biochem., 250, 745-750, 1997).

Method 2.

The pH of insect cell medium (10ml) containing procathepsin S was adjusted to 4.5 with glacial acetic acid and DTT and EDTA added to 5mM. The sample was then incubated at 37°C for 150min to enable conversion to the active enzyme. Ammonium sulphate was then added to 80% saturation and a pellet obtained by centrifugation. This pellet was redissolved in

2ml buffer A (100mM Tris, 500mM NaCl, 1mM EDTA, pH7.5) and mixed in a batchwise fashion with 100µl thiopropyl-Sepharose for 15min at 4°C. The non bound fraction was removed by a brief centrifugation and the gel washed with 2x1ml buffer A. Cathepsin S was then eluted by batch mixing with 0.4ml 20mM DTT in buffer A for 15min at 4°C.

Measurement of Cathepsin S Activity.

Cathepsin S activity was measured based on the method of Maubach et al (Eur. J. Biochem., 250, 745-750, 1997), using the fluorogenic substrate Z-Val-Val-Arg-NHMec. Inhibitors were identified by their ability to decrease the generation of the fluorescent leaving group (NHMec). Briefly the assay was as follows:

rHuman Cathepsin S (1.5 nmoles) was pre-incubated with or without compounds in 50mM Potassium phosphate buffer pH 6.0-6.2, 20mM Na_2EDTA, 0.1% BRIJ™ at 25°C for 5 minutes in a solid black 96 well plate. Synthetic substrate, 20µM Z-Val-Val-Arg-NHMec, was added and the mixture incubated at 30°C for 20 minutes. The reaction was stopped by the addition of 0.1M sodium chloroacetate pH 4.3. Fluorescence was determined using a Fluoroskan II plate reader; excitation 355nm, emission 460nm. Compound potency was determined from the raw fluorescence data by calculating the IC_{50} against Cathepsin S using a PC graph drawing software package.

The following results were obtained on a standard *in-vitro* test system for the inhibition of Cathepsin L. The activity is described in terms of IC_{50}.

When tested in the above *in-vitro* tests the compounds of this invention give IC_{50}s in the range 1-10,000 nM.

The following data was obtained for Examples 5, 105 and 120:

Example	IC_{50} (Human)	IC_{50} (Rabbit)
5		581.38
105	499	499.18
120	756	

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or

ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as the solvent unless otherwise stated;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in percentage by volume;

(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported; and

(xi) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations.

Example 1

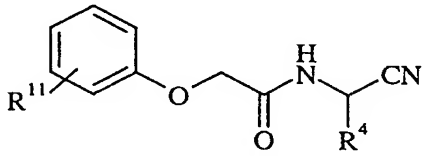
2-[2-(2,3-Dichlorophenoxy)acetamido]-2-(fur-2-yl)acetonitrile

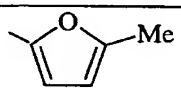
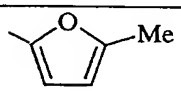
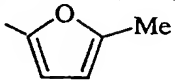
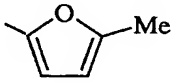
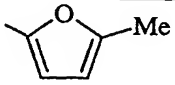
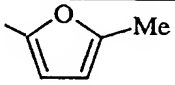
Oxalyl chloride (0.39 g) was added to a suspension of 2,3-dichlorophenoxyacetic acid (0.69 g) in dichloromethane (20 ml). One drop of *N,N*-dimethylformamide was added and the mixture was allowed to stir at ambient temperature for 14 hours. The solvent was removed under vacuum and the residue was dissolved in dichloromethane (10 ml). This solution of acid chloride was added to a mixture of 2-(2-furyl)-aminoacetonitrile (0.5 g) and triethylamine

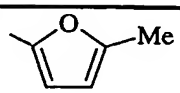
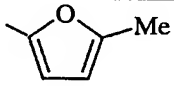
(0.63 g) in dichloromethane (10 ml) and was cooled in an ice bath. The reaction mixture was allowed to warm to ambient temperature and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica) eluted with dichloromethane to give 2-[2-(2,3-dichlorophenoxy)acetamido]-2-(fur-2-yl)acetonitrile (the title compound) 0.65 g. Mp 112°C; NMR: 4.82 (s, 2H), 6.33 (d, 1H), 6.55 (m, 2H), 7.0 (dd, 1H), 7.29 (m, 2H), 7.77 (m, 1H), 9.48 (d, 1H).

Examples 2 - 19

The following analogues were prepared according to the method of Example 1 using the appropriate acids and substituted aminoacetonitriles:

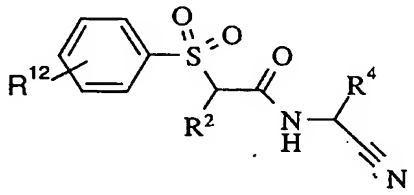


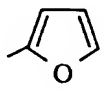
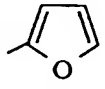
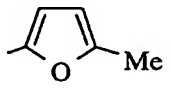
Example	R^{11}	R^4	Mp (°C)
2	2-Cl	2-furyl	78
3	4-MeO	2-furyl	105
4	2,4-diCl		60-61
5	2,6 di-Cl		59-61
6	2-Cl		79-81
7	2,3 di-Cl		74-76
8	2-Me		73-75
9	2-NO_2		85-86

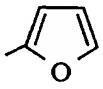
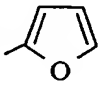
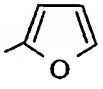
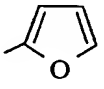
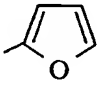
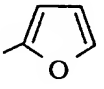
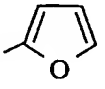
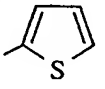
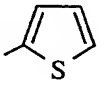
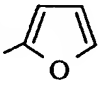
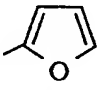
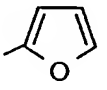
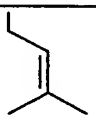
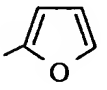
10	4-CH_3CONH-		136
11	2,6 di-Me		88-89
12	2-F	2-furyl	59-60
13	2-Br	2-furyl	72-73
14	2,4 di-Cl	2-(2-pyridyl)	149
15	2,4 di-Cl	2-(3-pyridyl)	136
16	2,4 di-Cl	2-(4-pyridyl)	157
17	2,4 di-Cl	3-furyl	74
18	2,4 di-Cl	2-thienyl	134
19	2,6 di-Br	2-furyl	93-94
20	2,4,6-trichloro	2-furyl	105-6

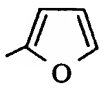
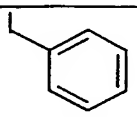
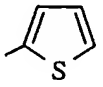
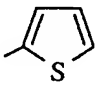
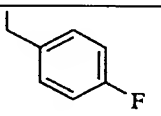
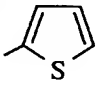
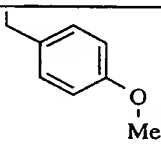
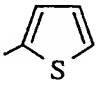
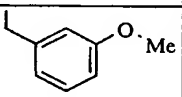
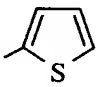
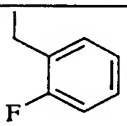
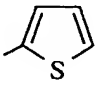
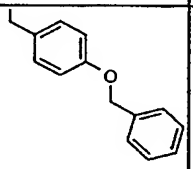
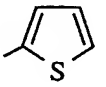
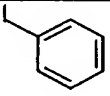
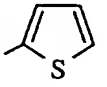
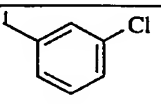
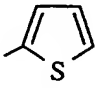
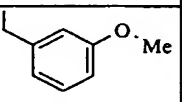
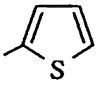
Example 21 - 59

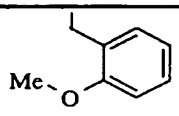
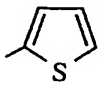
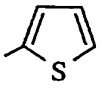
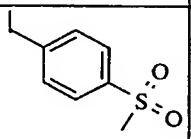
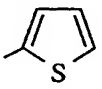
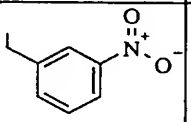
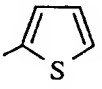
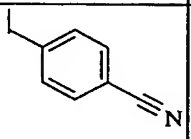
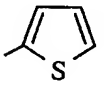
The following analogues were prepared according to the method of Example 1 using the appropriate sulphur containing acids and substituted aminoacetonitriles:

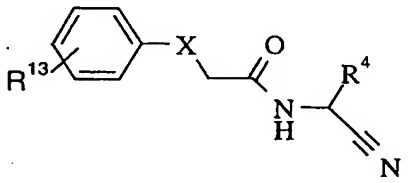


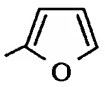
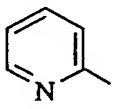
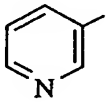
Example	R^{12}	R^2	R^4	Mp (°C)	MH^+
21	H	H		135-6	
22	4-Cl	H		90-95	
23	2,4-diCl	H			387

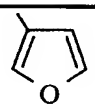
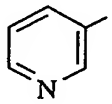
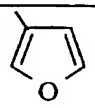
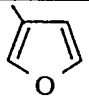
24	3-Cl	H		125.5-127	
25	2-Me	H			319
26	2-MeO	H		41-2. .	
27	2-Cl	H		112-114	
28	2-F	H		95-6	
29	3-F	H		139-40	
30	3-Cl	Me		118-20	
31	2,4-diCl	H		115	
32	2-Cl	H		103-4	
33	4-Me	H		120-1	
34	2-Br	H		105-6	
35	4-[$(Me)_2NCH_2$]	H			362
36	2-Cl				407

37	4-MeO	H			335
38	2-Cl			143-4	
39	4-MeO	H		84-5	
40	2-Cl			153-4	
41	2-Cl			116-7	
42	2-Cl			155-156	
43	2-Cl			107-8	
44	2-Cl			56-7	
45	H			175-6	
46	2-Cl			109-10	
47	H			174-5	

48	2-Cl			57-8	
49	2-Cl			42-3	
50	H			158-9	
51	H			156-8	
52	H			170-1	

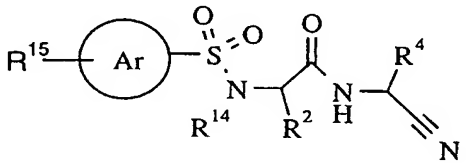


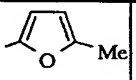
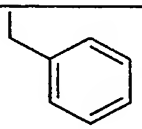
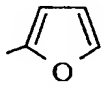
Example	X	R^{13}	R^4	Mp (°C)	MH^+
53	S	4-Cl		91	
54	$S(O)_2$	2,4-diCl		147	
55	$S(O)_2$	2,4-diCl			383

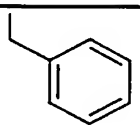
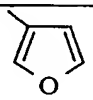
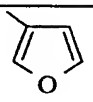
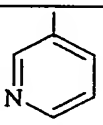
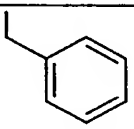
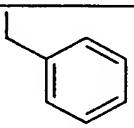
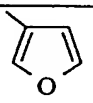
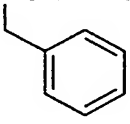
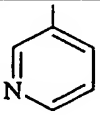
56	$S(O)_2$	2,4-diCl		109	
57	$S(O)_2$	2-Cl		132-3	
58	$S(O)_2$	2-Me		102-3	
59	$S(O)_2$	2-Cl		105-6	

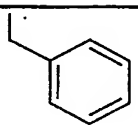
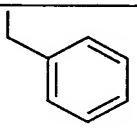
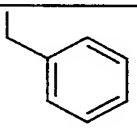
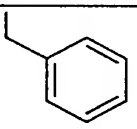
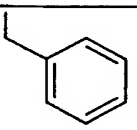
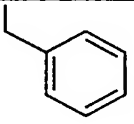
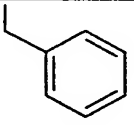
Examples 60 – 131 and 159-167

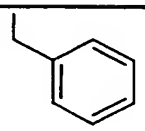
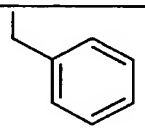
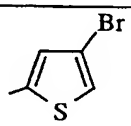
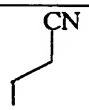
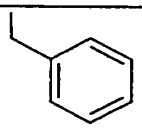
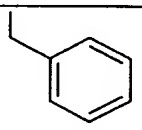
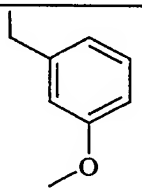
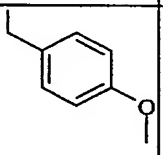
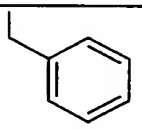
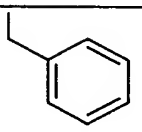
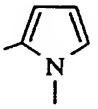
Examples 60-131 were prepared according to the method of Example 1 using the appropriate sulphonamide containing acids and substituted aminoacetonitriles. Examples 159-167 were prepared by adapting a suitable method disclosed herein.

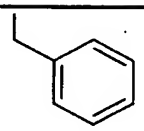
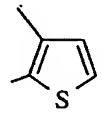
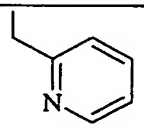
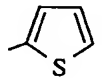
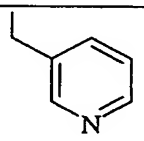
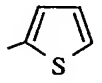
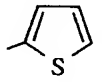
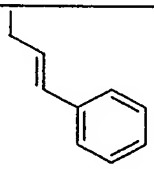
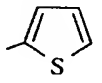
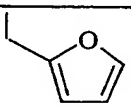
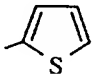
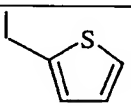
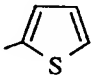
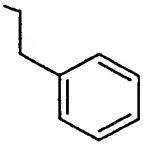
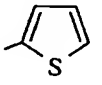
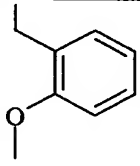
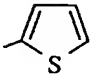


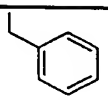
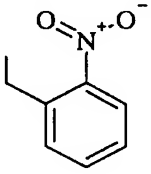
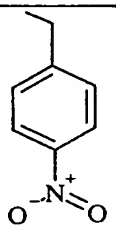
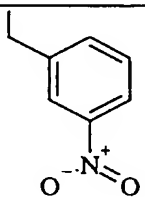
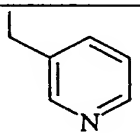
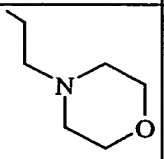
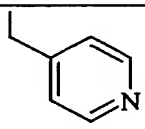
Example	Ar	R^{15}	R^{14}	R^2	R^4	Mp (°C)	MH^+
60	Ph	2,6-diCl	H	H			402
61	Ph	4-Cl		H		135	
62	Ph	2,4-diCl	Me	H			403
63	Ph	4-Cl	H	H			354

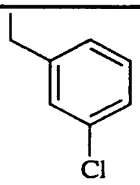
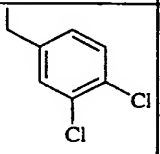
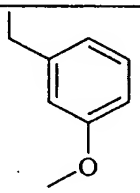
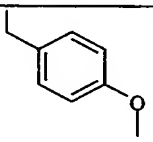
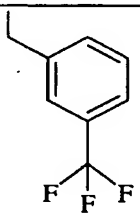
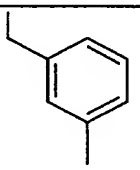
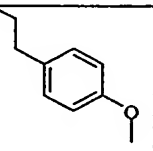
64	Ph	2,4-diCl		H		121	
65	Ph	4-Cl	Me	H		153	
66	Ph	4-Cl		H		100	
67	Ph	4-Cl	Me	H		170	
68	Ph	4-Cl	Me	H		159	
69	Ph	2-Cl	Me	H			368
70	Ph	2-Cl	Me	H			368
71	Ph	2-Cl	Me	H			379
72	Ph	2-Cl	Me	H			384
73	Ph	2-Cl		H		112	
74	Ph	2-Cl		H		115	
75	Ph	2-Cl		H			455

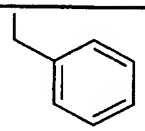
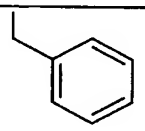
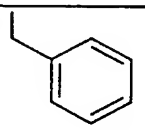
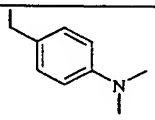
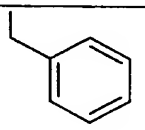
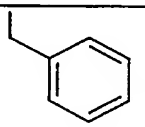
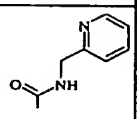
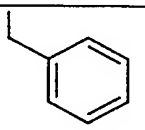
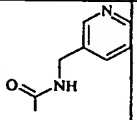
76	Ph	2-Cl		H		105	
77	Ph	2-Cl		H		110	
78	Ph	2-Cl		H		134	
79	Ph	2-Br		H		110	
80	Ph	2-Br		H		115	
81	Ph	2-Br		H		132	
82	Ph	2-Br		H		155	
83	Ph	2-NO_2		H		108	
84	Ph	2-NO_2		H		117	
85	Ph	2-CF_3		H		129	
86	Ph	2-F		H		109	

87	Ph	2-F		H		88	
88	Ph	2,4-diCl		H			574
89	Ph	2-Cl		H			423
90	Ph	2,4-diF		H		112	
91	Ph	2,4-diF		H		113	
92	Ph	2-F		H		110	
93	Ph	2-F		H		160	
94	Ph	H		H		125	
95	Ph	2-F		H		186	

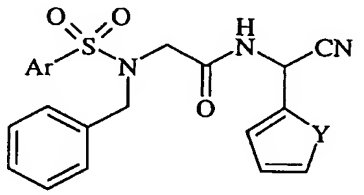
96	Ph	2-F		H		138	
97	Ph	2-F		H		125	
98	Ph	2-F		H		130	
99	Ph	2-F	Et	H		78	
100	Ph	2-F		H		106	
101	Ph	H		H		108	
102	Ph	H		H		88	
103	Ph	H		H		138	
104	Ph	H		H		81	

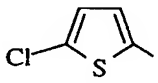
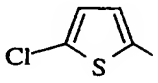
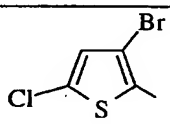
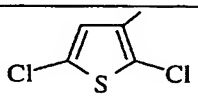
105	Ph	H	H			178	
106	Ph	H		H		16	
107	Ph	H		H		115	
108	Ph	H		H		75	
109	Ph	H		H		114	
110	Ph	H		H		150	
111	Ph	H		H		110	

112	Ph	H		H		112	
113	Ph	H		H		144	
114	Ph	H		H		99	
115	Ph	H		H		136	
116	Ph	H		H		72	
117	Ph	H		H		135	
118	Ph	H		H		119	

119	Napth-3-yl	H		H		137	
120	Napth-1-yl	H		H		157	
121	Napth-1-yl	5-$(CH_3)_2N$		H		86	
122	Ph	H		H			469
123	Ph	H		H	EtOC(O)	107	
124	Ph	H		H		126	
125	Ph	H		H		160	
126	Ph	H	H			89	
159	Ph	H	H	iso-Propyl	2-thienyl	162-165	
160	Ph	H	H	(3-indolyl)-CH_2	2-thienyl		465
161	Ph	H	H	benzyl	2-thienyl		412
162	Ph	H	H	$(CH_2)_4N(H)CHO$	2-thienyl		435
163	Ph	H	H	CH_2cyclohexyl	2-thienyl		432
164	Ph	H	H	t-Butyl	2-thienyl		
165	Ph	H	H	n-Butyl	2-thienyl		

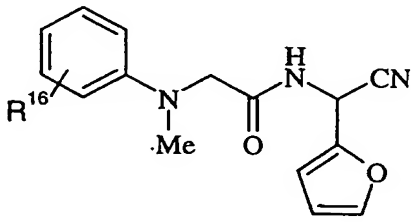
166	Ph	H	H	$Ph(CH_2)_2$	2-thienyl		440
167	Ph	H	H	D-2-methyl-n-Propyl	2-thienyl		392



Example	Ar	Y	Mp (°C)
127		O	127
128		S	88
129		S	146
130		S	153
131		S	130

Example 132

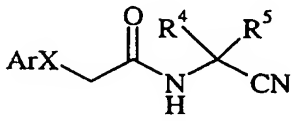
The following analogue was prepared according to the method of Example 1 using the appropriate (substituted phenyl)-N-methylglycines and substituted aminoacetonitriles:



Example	R^{16}	MH^+
132	2,4 di-Cl	338

Examples 133 - 139

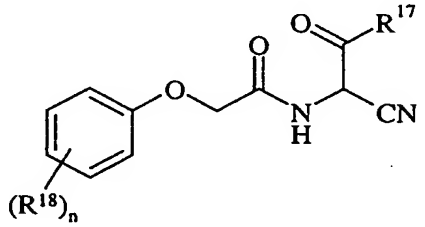
The following analogues were prepared according to the method of Example 1 using the appropriate starting materials:



Example	Ar	X	R^4	R^5	Mp (°C)	MH^+
133	2,4,6-trichlorophenyl	O	H	H	116-118	293
134	2,4-dichlorophenyl	O	H	H		259
135	2,4,5-trichlorophenyl	O	H	H		293
136	pentachlorophenyl	O	H	H	154-157	361
137	2,4,6-trichlorophenyl	O	Me	Me	109-110	321
138	2,4-dichlorophenyl	O	MeOC(O)-	H		317
139	2-naphthyl	S	H	H		257

Examples 140 - 144

The following analogues were prepared according to the method of Example 1 using the appropriate starting materials:



Example	$(R^{18})_n$	R^{17}	Mp (°C)
140	2,4-diCl	EtO-	119-20
141	2-Cl	EtO-	100-1
142	2,4-diCl	^{n}PrNH-	161-2
143	2,4-diCl	^{i}BuNH-	162-3
144	2,4-diCl	$PhCH_2NH$-	194-5

Example 145

2-[2-(2-Naphthylsulphonyl)acetamido]-acetonitrile

A mixture of 2-[2-(2-naphthylthio)acetamido]-acetonitrile (130 mg), methanol (2 ml), tetrahydrofuran (2 ml), oxone (500 mg) and water (1 ml) was stirred at room temperature for 24 hours. The mixture was made up to a volume of 20 ml by diluting with water and the precipitate was collected, dried and recrystallised from ethyl acetate to give 2-[2-(2-naphthylsulphonyl)acetamido]-acetonitrile (130 mg). M/z 289 (MH^+); ^1H NMR 4.15 (d, 2H), 4.45 (s, 2H), 7.75 (m, 2H), 7.85 (dd, 1H), 8.1 (d, 1H), 8.2 (m, 2H), 8.55 (s, 1H), 8.95 (m, 1H).

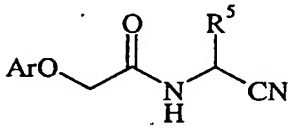
Example 146

2-[2-(2,4,6-Trichlorophenoxy)acetamido]-2-methoxyacetonitrile

Trifluoroacetic anhydride (0.12 ml) was added dropwise to a stirred mixture of 2-[2-(2,4,6-trichlorophenoxy)acetamido]-2-methoxyacetamide (98 mg) in pyridine (3 ml) at -15°C.The mixture was allowed to warm to ambient temperature then poured into ice-water and extracted with ether. The organic phase was washed with brine, dried and evaporated to dryness under reduced pressure to give 2-[2-(2,4,6-trichlorophenoxy)acetamido]-2-methoxyacetonitrile (70 mg). Mp 123-124°C; m/z 323 (MH^+); ^1H NMR 3.35 (s, 3H), 4.55 (s, 2H), 6.02 (d, 1H), 7.72 (s, 2H), 9.90 (d, 1H).

Examples 147 - 150

The following analogues were prepared according to the method of Example 146 using the appropriate starting materials:



Example	Ar	R^5	Mp (°C)	MH^+
147	2,4-dichlorophenyl	methoxy	130-132	228M+
148	2,4,6-trichlorophenyl	isopropylthio	58-59	367
149	2,4-dichlorophenyl	isopropylthio	94-95	333
150	2,4-dichlorophenyl	methylthioethyl	-	333

Example 151

2-[2-(2,4-Dichlorophenoxy)acetamido]-2-prop-2-ynyloxy acetonitrile

N-bromosuccinimide (42 mg) was added to a stirred solution of 2-[2-(2,4-dichlorophenoxy)acetamido]-2-isopropylthio acetonitrile (52 mg) in propargyl alcohol (1.5 ml). The mixture was allowed to warm to room temperature and evaporated to dryness under reduced pressure and the residue was partitoned between ethyl acetate and water. The organic phase was separated, dried and evaporated to dryness under reduced pressure. The residue was purified by medium pressure liquid chromatography on silica using increasingly polar mixtures of ether and hexane as eluent to give 2-[2-(2,4-dichlorophenoxy)acetamido]-2-prop-2-ynyloxy acetonitrile (24 mg). Mp 74-75°C; m/z 312 (M^+); ^{1}H NMR ($CDCl_3$) 3.4 (t, 1H), 4.3 (d, 2H), 4.8 (s, 2H), 6.15 (d, 1H), 7.05 (d, 1H), 7.4 (dd, 1H), 7.6 (d, 1H), 9.85 (d, 1H).

Example 152

N-(4-Morpholino)ethyl-2-cyano-2-[2-(2,4-dichlorophenoxy)acetamido]acetamide

A mixture of methyl-2-(2,4-dichlorophenoxy)acetamido-2-cyano acetate (100 mg), acetonitrile (0.5 ml) and 4-aminoethylmorpholine was stirred at ambient temperature for 2 hours. The mixture was evaporated to dryness under reduced pressure and the residue was purified by medium pressure liquid chromatography on silica using increasingly polar mixtures of ethyl acetate and chloroform as eluent followed by trituration with ether/hexane to give *N*-(4-morpholino)ethyl-2-cyano-2-[2-(2,4-dichlorophenoxy)acetamido]acetamide (70 mg). M/z 415 (MH^+); ^{1}H NMR ($CDCl_3$,ppm) 2.4-2.65 (m, 6H), 3.45 (m, 2H), 3.75 (m, 4H), 4.6 (m, 2H), 5.4(d, 1H), 6.85 (m, 2H), 7.25 (m, 1H), 7.8 (d, 1H).

Example 153

4-Chlorophenylsulphinylacetyl-2(2-furyl)-acetonitrile

Sodium metaperiodate (0.33 g) in water (5 ml) was added to a solution of 4-chlorophenylthioacetyl-2(2-furyl)-acetonitrile (0.4 g) in methanol (30 ml) and the mixture was stirred at ambient temperature for 14 hours. The reaction mixture was diluted with water (100 ml) and extracted with diethyl ether (3 x 50 ml) and dried. The residue obtained on removal of the solvent was subjected to chromatography, eluting with a mixture of ethyl acetate and dichloromethane (1:20 v/v) to give 4-chlorophenylsulphinylacetyl-2(2-furyl)-acetonitrile, 0.18 g. Mp 124 °C; $C_{14}H_{11}ClN_2O_3S$ requires C, 52.1%; H, 3.4%; N, 8.7%. Found; C, 52.3%; H, 3.4%; N, 8.7%. ^{1}H NMR 3.91 (m, 2H), 6.28 (dd, 1H), 6.55 (m, 2H), 7.68 (m, 4H), 7.77 (m, 1H), 9.50 (d, 1H).

Example 154

2-Cyano-2-[2-(2,4-dichlorophenoxy)acetyl]aminoacetamide

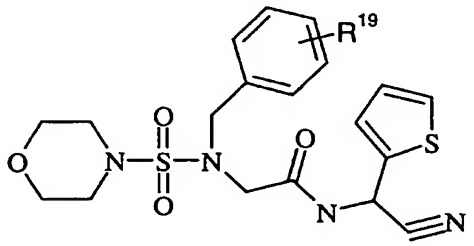
A mixture of 2,4-dichlorophenoxyacetic acid (1.12 g), 2-amino-2-cyanoacetamide (0.5 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.06 g) and hydroxybenzotriazole (0.75 g) in *N,N*-dimethylformamide (20 ml) was stirred at ambient temperature for 18 hours. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (2 x 75 ml). The ethyl acetate extracts were washed with 2M hydrochloric acid, water, saturated aqueous sodium bicarbonate and brine and dried over magnesium sulphate. Removal of the solvent gave a solid which was washed with an acetone-diethyl ether mixture and air dried to give 2-cyano-2-[2-(2,4-dichlorophenoxy)acetyl]aminoacetamide, yield 1.1 g. Mp 190-193°C; m/z 302 (MH^+).

Example 155

2-Cyano-2-[2-(2,6-dichlorophenoxy)acetyl]aminoacetamide was also made by the procedure of Example 154. Mp 207-209°C.

Examples 156-158

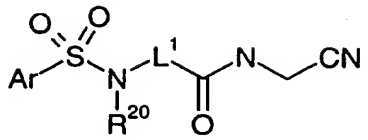
The following analogues were prepared according to the method of Example 1 using the appropriate starting materials:



Ex No.	R^{19}	Mp (°C)	MH^+
156	H	110	435.5
157	3-CF_3	gum	503
158	3-NO_2	gum	480.5

Examples 168-176

The following Examples were prepared by adapting a suitable method hereinbefore disclosed using appropriate starting materials.



Example	Ar	R^{20}	L^1	Mp	M+H
168	1,3-di-Me-5-Cl-pyrazol-4-yl	CH_2Ph	CH_2	155	
169	4-Ph-Ph	CH_2Ph	CH_2	118	
170	6-Cl-imidazo[2,1-b]thiazol-5-yl	H	CH-cyclohexyl	155	
171	1-Me-4-imidazolyl	H	CH-cyclohexyl	170	
172	5-(2-Me-thiazol-4-yl)-2-thienyl	CH_2Ph	CH_2	157	
173	5-(5-CF_3-1-Me-pyrazol-3-yl)-2-thienyl	CH_2Ph	CH_2	124	
174	5-(2-pyridyl)-2-thienyl	CH_2Ph	CH_2	154	
175	3-CF_3-$PhCH_2$	CH_2Ph	CH_2		426
176	1,2-di-Me- imidazol-4-yl	CH_2Ph	CH_2		362

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions (Methods A-M) are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method A

2-(2-Furyl)-aminoacetonitrile hydrochloride

Ammonium chloride (25 g) was added to a solution of 2-furfuraldehyde (25 g) in diethyl ether (250 ml). A solution of sodium cyanide (17 g) in water (80 ml) was added over 20 minutes. The reaction mixture was stirred at ambient temperature for 14 hours , the aqueous layer was removed and the organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 100 ml), dried and evaporated to dryness. The residue was dissolved in diethyl ether (250 ml) and cooled to 0°C. Hydrogen chloride gas was bubbled through the solution keeping the temperature below 10°C. 2-(2-Furyl)-aminoacetonitrile hydrochloride (the title compound) was filtered and dried, yield 33 g. ^{1}H NMR 6.19 (s, 1H), 6.56 (m, 1H), 6.78 (d, 1H), 7.83 (m, 1H), 9.83 (broad s, 2H).

Methods A1-4

Following the method outlined in Method A and using the appropriate aldehyde there was prepared:

A1 2-[2-(5-methylfuryl)]-aminoacetonitrile hydrochloride;

A2 2-(3-furyl)-aminoacetonitrile hydrochloride;

A3 2-(2-thienyl)-aminoacetonitrile hydrochloride;

A4 2-[2-(4-bromothienyl)]-aminoacetonitrile hydrochloride.

Method B

2-(2-Pyridyl)-aminoacetonitrile hydrobromide

2-Pyridine carboxaldehyde (25 g) was added over 30 minutes to a cooled (0°C) solution of sodium cyanide (12.6 g) in water (75 ml). The mixture was stirred at 0 °C for 10 minutes and acetic acid (15.5 g) was added over 30 minutes. The mixture was stirred at ambient temperature for 14 hours and the solid 2-hydroxy-2-(2-pyridyl)-acetonitrile was filtered and dried. The solid cyanohydrin was added to a cooled (0°C) solution of ammonium chloride (60.9 g) and ammonia (31 ml) in water (170 ml) and the mixture was stirred at ambient temperature for 14 hours. The solid was filtered and washed with water (3 x 100 ml). The combined aqueous extracts were washed with dichloromethane (7 x 100 ml). The dichloromethane extracts were dried and the solvent removed under reduced pressure. The residue was suspended in diethyl ether (200 ml) and HBr in acetic acid was added. The solid 2-(2-pyridyl)-aminoacetonitrile hydrobromide was filtered and washed with diethyl ether (4 x 50 ml) and dried under vacuum, yield 4.7 g.

Methods B1-2

Following the method outlined in Method B and using the appropriate cyanohydrin there was prepared:

B1 2-(3-pyridyl)-aminoacetonitrile hydrochloride, Mp 148 °C;

B2 2-(4-pyridyl)-aminoacetonitrile hydrochloride.

Method C

Pentachlorophenoxy acetic acid

A mixture of pentachlorophenol (5 g), acetone (80 ml), methyl bromoacetate (1.74 ml) and potassium carbonate (7.8 g) was stirred at reflux for 3 hours, cooled, filtered and the filtrate was evaporated to dryness under reduced pressure to give methyl-2-(pentachlorophenoxy)acetate (6.27 g). M/z 336 (M^+) which was used without further purification.

A mixture of methyl-2-(pentachlorophenoxy)acetate (2 g), tetrahydrofuran (12 ml), methanol (10 ml) and 4M sodium hydroxide (4.6 ml) was stirred at ambient temperature for 3 hours. The solution was concentrated to 5 ml under reduced pressure, diluted with water and

acified with glacial acetic acid. The precipitate was collected ,washed with water and dried to give pentachlorophenoxy acetic acid (1.89 g). M/z 322 (M^+).

Method D

2-[2-(2,4,6-Trichlorophenoxy)acetamido]-2-methoxyacetamide

A mixture of 2,4,6-trichlorophenol (7.5 g), acetone (150 ml), methyl bromoacetate (3.52 ml) and potassium carbonate (15.72 g) was stirred at reflux for 3 hours, cooled and filtered. The filtrate was evaporated to dryness under reduced pressure to give methyl-2-(2,4,6-trichlorophenoxy)acetate (10.2 g). M/z 268 (M^+) which was used without further purification.

A mixture of methyl-2-(2,4,6-trichlorophenoxy)acetate (10.1 g), methanol (30 ml) and concentrated aqueous ammonia (50 ml) was stirred at ambient temperature for 16 hours. The insoluble solid was collected washed with water, dried and evaporated to dryness under reduced pressure to give 2-(2,4,6-trichlorophenoxy)acetamide (8.52 g). M/z 254 (MH^+).

A mixture of glyoxilic acid monohydrate (1.5 g) and dichloroethane (50 ml) was stirred at reflux until the volume had been reduced to 25 ml. 2-(2,4,6-trichlorophenoxy)acetamide (4.1 g) was added and the mixture stirred at reflux for 5 hours, cooled, and the insoluble solid collected to give 2-[2-(2,4,6-trichlorophenoxy)acetamido]-glycolic acid (2.98 g). M/z 328 (MH^+) which was used without further purification.

Thionyl chloride (4 ml) was added to a stirred solution of 2-[2-(2,4,6-trichlorophenoxy)acetamido]glycolic acid (500 mg) in 1:1 dichloromethane:tetrahydrofuran (10 ml) and the mixture was stirred at ambient temperature under argon for 2.5 hours and then evaporated to dryness under reduced pressure. The residue was dissolved in methanol and the mixture was stirred at ambient temperature under argon for 0.3 hours and then evaporated to dryness under reduced pressure. The residue was treated with concentrated aqueous ammonia (20 ml) and the mixture was stirred at ambient temperature for 18 hours. The insoluble solid was collected and purified by medium pressure liquid chromatography on silica using 2% methanol in dichloromethane as eluent to give 2-[2-(2,4,6-trichlorophenoxy)acetamido]-2-methoxyacetamide (100 mg). M/z 341 (MH^+).

Method D1

Following the method outlined in Method D and using the appropriate starting materials there was prepared:

D1 2-[2-(2,4,-dichlorophenoxy)acetamido]-2-methoxyacetamide. M/z 306 (MH^+).

Method E

2-[2-(2,4,6-Trichlorophenoxy)acetamido]-2-isopropylthio acetamide

Concentrated sulphuric acid (0.5 ml) was added to a stirred, ice cold mixture of 2-[2-(2,4,6-trichlorophenoxy)acetamido]glycolic acid (1 g), glacial acetic acid (5 ml) and 2-propanethiol (1.13 ml) and the mixture was kept at ambient temperature for 16 hours. The mixture was then treated with water and extracted with ethyl acetate. The extract was washed successively with water and brine, dried and evaporated to dryness under reduced pressure to give 2-[2-(2,4,6-trichlorophenoxy)acetamido]-2-isopropylthio acetic acid (1.29 g) which was used without further purification. M/z 386 (MH^+).

A mixture of 2-[2-(2,4,6-trichlorophenoxy)acetamido]-2-isopropylthio acetic acid (1.14 g), methanol (7 ml) and concentrated sulphuric acid (0.2 ml) was stirred at ambient temperature for 4 hours. The mixture was basified with aqueous sodium bicarbonate and the resulting mixture was extracted with ethyl acetate and the extract was dried and evaporated to dryness under reduced pressure to give methyl-2-[2-(2,4,6-trichlorophenoxy)acetamido]-2-isopropylthio acetate (1.29 g) which was used without further purification. M/z 400 (MH^+).

A mixture of methyl-2-[2-(2,4,6-trichlorophenoxy)acetamido]-2-isopropylthio acetate (0.99 g) and concentrated aqueous ammonia (20 ml) was stirred at ambient temperature for 18 hours. The insoluble solid was collected and washed with water to give 2-[2-(2,4,6-trichlorophenoxy)acetamido]-2-isopropylthio acetamide (0.79 g). M/z 385 (MH^+) which was used without further purification.

Method E1

Following the method outlined in Method E and using the appropriate starting materials there was prepared:

E1 2-[2-(2,4-dichlorophenoxy)acetamido]-2-isopropylthio acetamide. M/z 351 (MH^+).

Method F

(2S)-2-[2-(2,4-Dichlorophenoxy)acetamido]-4-methylthiobutyramide

2,4-Dichlorophenoxyacetylchloride (1.2 g) was added dropwise to a stirred, ice cooled mixture of 2-S-methionine amide hydrochloride (0.91 g), *N,N*-dimethylformamide (10 ml) and 4-methyl morpholine (0.8 ml) was stirred at ambient temperature for 2 hours. Water was added and the mixture was extracted with chloroform. The extract was washed successively with water, 1M hydrochloric acid and brine, dried and evaporated to dryness under reduced

pressure. The residue was triturated with ether and the insoluble solid collected to give (2S)-2-[2-(2,4-dichlorophenoxy)acetamido]-4-methylthiobutyramide (1.25 g). M/z 351 (MH^+).

Method G

Ethyl (3-chlorophenylthio)acetate

A mixture of 3-chlorothiophenol (6.0 g) and potassium carbonate (7.45 g) in acetone (50 ml) was stirred at ambient temperature for 30 minutes then ethyl bromoacetate (6.06 ml) was added. The mixture was stirred for 14 hours and filtered. The filtrate was evaporated to dryness and the residue was subjected to chromatography, eluting with a mixture of dichloromethane and isohexane (1:1, v/v) to give ethyl (3-chlorophenylthio)acetate, 9.22 g, as an oil. M/z 231 $(MH)^+$.

Method H

Ethyl 3-chlorophenylsulphonylacetate

A solution of ethyl (3-chlorophenylthio)acetate (3.5 g) in dichloromethane (75 ml) was cooled to 0°C in an ice bath and m-chloroperbenzoic acid (3.16 g) was added in portions. The mixture was stirred for 3 hours and a further portion of m-chloroperbenzoic acid (3.16 g) was added. The mixture was stirred for 2 hours and filtered. The filtrate was washed successively with aqueous 5% sodium thiosulphate solution (3 x 50 ml), saturated aqueous sodium bicarbonate (3 x 50 ml) and brine (50 ml) and dried. The oil obtained on removal of the solvent was subjected to chromatography, eluting with a mixture of dichloromethane and isohexane (1:1, v/v) to give ethyl 3-chlorophenylsulphonylacetate, 2.92 g, as an oil. M/z 280 $(M+NH_4)^+$.

Method I

3-Chlorophenylsulphonylacetic acid

A mixture of ethyl 3-chlorophenylsulphonylacetate (2.9 g) and aqueous 2M sodium hydroxide solution (28 ml) in a mixture of methanol (20 ml) and tetrahydrofuran (30 ml) was stirred at ambient temperature for 14 hours. The solvent was removed under reduced pressure and water (10 ml) was added to the residue which was acidified to pH 1-2 with concentrated HCl. 3-Chlorophenylsulphonylacetic acid was filtered and dried, yield 2.5 g.

Method J

Ethyl 2-(3-chlorobenzyl)-2-(2-chlorophenyl)sulphonyl acetate

Sodium hydride (0.25 g) was added to a solution of ethyl 2-chlorophenylsulphonylacetate (1.50 g) in *N,N*-dimethylformamide (75 ml) and the mixture

was stirred for 30 minutes. 3-Chlorobenzyl bromide (0.83 ml) was added and the mixture was stirred for 14 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (75 ml) and washed with 2M hydrochloric acid (3x 25 ml) and water (25 ml) then dried. The oil obtained on removal of the solvent was subjected to chromatography, eluting with a mixture of dichloromethane and isohexane (1:1, v/v) to give ethyl 2-(3-chlorobenzyl)-2-(2-chlorophenyl)sulphonyl acetate, 1.74 g. M/z 387 (MH^+).

Method K

N-(N-Morpholinosulphonyl)-N(benzyl)glycine

N-(N-Morpholinosulphonyl)-N(benzyl)glycine methyl ester (Method L) (1.3 g) was dissolved in ethanol (25 ml) and aqueous 2M sodium hydroxide (9.9 ml) was added and the mixture stirred at ambient temperature for 20 hours. The reaction mixture was reduced to small volume, diluted with water (25 ml) , acidified with 2M HCl and extracted with dichloromethane (3x25 ml). The combined dichloromethane extracts were dried. The solvent was removed and the residue was triturated with isohexane to give the title compound, 0.9g. Mp 168 °C; NMR: 7.3 (m, 4H), 4.49 (s, 2H), 3.75 (s, 2H), 3.58 (m, 4H), 3.1 (m, 4H).

Method L

N-(N-Morpholinosulphonyl)-N(benzyl)glycine methyl ester

A mixture of N-(N-morpholinosulphonyl)glycine methyl ester (Method M) (1.4 g), benzyl bromide (1.06 g) and potassium carbonate (0.83 g) in acetonitrile (10 ml) was stirred at ambient temperature for 24 hours. The reaction mixture was filtered and the filtrate was evaporated to dryness and the residue obtained was chromatographed on silica eluting with a mixture of ethyl acetate and isohexane (1/1 v/v) to give the title compound, 1.3g. NMR ($CDCl_3$): 7.3 (m, 5H), 4.95 (s, 2H), 3.85 (s, 2H), 3.7 (m, 7H), 3.3 (m, 4H).

Following the procedure of Methods K and L and using the appropriate starting materials, the following compounds were prepared:

N-(N-morpholinosulphonyl)-N-(3-trifluoromethylbenzyl)glycine

N-(N-morpholinosulphonyl)-N-(3-nitrobenzyl)glycine.

Method M

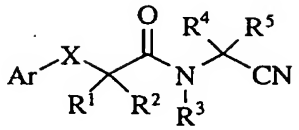
N-(N-Morpholinosulphonyl)glycine methyl ester

Glycine methyl ester hydrochloride (9.2 g) was added to a 1M solution of sulphuryl chloride in dichloromethane (73 ml) and the mixture was cooled to -78 °C. A solution of

triethylamine (7.3 g) in dichloromethane (100 ml) was added dropwise over 1 hour. The mixture was stirred at -78 °C for 1 hour then morpholine (6.2 g) and triethylamine (7.3 g) were added and the mixture was allowed to warm to ambient temperature. The reaction mixture was washed with water (3x100 ml), dried and the residue obtained on removal of the solvent was triturated with ether to give a solid which was filtered. The filtrate was evaporated to dryness to give the title compound, 4.3 g. NMR ($CDCl_3$): 5.1 (bs, 1H), 3.85 (d, 2H), 3.75 (s, 3H), 3.65 (m, 4H), 3.2 (m, 4H).

CLAIMS

1. A compound of formula (I):



(I)

wherein **Ar** is optionally substituted phenyl, optionally substituted naphthyl, Het, C_{3-12} cycloalkyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^6S-, $R^6C(O)$- and R^6CH_2-; $\mathbf{R^6}$ is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; with the proviso that when Ar is a nitrogen linked Het, X is not –N(R^7)- or –O-; **X** is -N(R^7)-, -S(O)$_n$-, -O- or -SO_2N(R^7)-; **n** is 0, 1 or 2; $\mathbf{R^7}$ is H, C_{1-6}alkyl (optionally substituted with one or more of cyano, Het and R^{10}), C_{2-6}alkenyl (optionally substituted with R^{10}) or formyl; $\mathbf{R^{10}}$ is an optionally substituted five or six membered heteroaryl ring, optionally substituted phenyl or optionally substituted naphthyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl,

C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkoxy; **R^1** is H, C_{1-6}alkyl (optionally substituted with R^8), C1-6 alkylsulphanyl (optionally substituted with R^8), C_{2-6}alkenyl, R^8 or R^8S-; **R^8** is phenyl, C_{3-12} cycloalkyl, Het or a 5- or 6- membered heteroaryl ring, all of which are optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and benzyloxy, with the proviso that if R^1 is C_{1-6} alkylsulphanyl (optionally substituted with R^8) or R^8S- then X is $-SO_2N(R^7)$-; **R^2** is H or C_{1-6}alkyl; **R^3** is H or C_{1-6}alkyl; **R^4** is H, C_{1-6}alkyl (optionally substituted with one or more of hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^9, R^9C_{1-6}alkylsulphanyl, R^9C_{1-6}alkylsulphinyl and R^9C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more of C_{2-6}alkenyl, C_{2-6}alkynyl, R^9, R^9C_{2-6}alkenyl, R^9C_{2-6}alkynyl, Het and trifluoromethyl), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^9-, R^9S-, R^9C_{1-6}alkylsulphanyl, *N*-(R^9C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; **R^9** is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; **R^5** is H or C_{1-6}alkyl; and, **Het** is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; provided that: when R^1 is H or C_{1-6} alkyl, X is O or S, and R^2 and R^3 are both hydrogen, then Ar is not pyrimid-4-yl; when R^1 and R^2 are both hydrogen, R^3 is C_{1-6} alkyl, X is O, R^4 is hydrogen, C_{1-6} alkyl, phenyl or benzyl, and R^5 is hydrogen or C_{1-4} alkyl, then Ar is not

halophenyl; when R^1 and R^3 are both hydrogen, R^2 and R^5 are, independently, hydrogen or methyl, R^4 is unsubstituted pyrrolyl, thienyl or furyl, and X is O, then Ar is not 3-methyl-2,4-dichlorophenyl; when R^1 is hydrogen or C_{1-4} alkyl, R^2 is hydrogen or C_{1-4} alkyl, R^3 is hydrogen, R^4 is hydrogen, C_{1-6} alkyl or phenyl, and X is O, S, NH or N(C_{1-4} alkyl), then Ar is not phenyl optionally substituted with: halo, C_{1-4} alkyl, CF_3, C_{1-4} alkoxy, CO_2H, $CO_2(C_{1-4}$ alkyl), $CONH_2$, NO_2, CN, $CH_2N(CH_3)_2$, $S(C_{1-4}$ alkyl) or mono- or di-chlorobenzyl; when R^1, R^2, R^3 and R^5 are all hydrogen, R^4 is $SO_2CH_2CH_3$, and X is SO_2, then Ar is not phenyl; and, when R^1, R^2, R^3, R^4 and R^5 are all hydrogen, and X is SO_2NH, then Ar is not 4-methylphenyl; or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein Ar is an optionally substituted phenyl, optionally substituted naphthyl, morpholino or an optionally substituted 5-membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, *N,N*-(C_{1-6}alkyl)$_2$amino and *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl with the proviso that when Ar is morpholino X cannot be -N(R^7)- or -O-.

3. A compound as claimed in claim 1 or 2 wherein X is -N(R^7)-, -S(O)$_n$-, -O- or -SO_2N(R^7)-; wherein n = 0-2; R^7 is H, C_{1-6}alkyl (optionally substituted with cyano, Het or R^{10}) or R^7 is C_{2-6}alkenyl (optionally substituted with R^{10}); R^{10} is an optionally substituted five or six membered heteroaryl ring or optionally substituted phenyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl and C_{1-6}alkoxy; and Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms.

4. A compound as claimed in claim 1, 2 or 3 wherein R^1 is hydrogen, C_{2-6}alkenyl or C_{1-6}alkyl which is optionally substituted with phenyl where said phenyl is optionally substituted by one or more groups chosen from halo, cyano, C_{1-6}alkoxy, nitro, C_{1-6}alkylsulphonyl and benzyloxy.

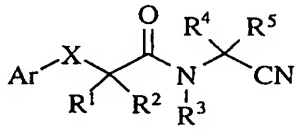
5. A compound as claimed in claim 1, 2, 3 or 4 wherein R^2 and R^3 are both hydrogen.

6. A compound as claimed in claim 1, 2, 3, 4 or 5 wherein R^5 is hydrogen or methyl.

7. A compound as claimed in any one of the preceding claims wherein R^4 is hydrogen, C_{1-6}alkyl (optionally substituted with C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl and C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with C_{2-6}alkynyl), C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkylsulphanyl, R^9- or N-(R^9C_{1-6}alkyl)carbamoyl; R^9 is phenyl or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl and halo; and Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms.

8. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 and a pharmaceutically acceptable diluent or carrier.

9. A compound of formula (I):



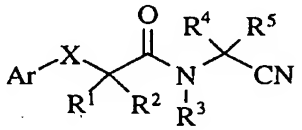
(I)

wherein **Ar** is optionally substituted phenyl, optionally substituted naphthyl, Het, C_{3-12} cycloalkyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^6S-, $R^6C(O)$- and R^6CH_2-; R^6 is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino,

C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; with the proviso that when Ar is a nitrogen linked Het, X is not –N(R^7)- or –O-; **X** is -N(R^7)-, -S(O)$_n$-, -O- or -SO_2N(R^7)-; **n** is 0, 1 or 2; $\mathbf{R^7}$ is H, C_{1-6}alkyl (optionally substituted with one or more of cyano, Het and R^{10}), C_{2-6}alkenyl (optionally substituted with R^{10}) or formyl; $\mathbf{R^{10}}$ is an optionally substituted five or six membered heteroaryl ring, optionally substituted phenyl or optionally substituted naphthyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkoxy; $\mathbf{R^1}$ is H, C_{1-6}alkyl (optionally substituted with R^8), C1-6 alkylsulphanyl (optionally substituted with R^8), C_{2-6}alkenyl, R^8 or R^8S-; $\mathbf{R^8}$ is phenyl, C_{3-12} cycloalkyl, Het or a 5- or 6- membered heteroaryl ring, all of which are optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and benzyloxy, with the proviso that if R^1 is C_{1-6} alkylsulphanyl (optionally substituted with R^8) or R^8S- then X is –SO_2N(R^7)-; $\mathbf{R^2}$ is H or C_{1-6}alkyl; $\mathbf{R^3}$ is H or C_{1-6}alkyl; $\mathbf{R^4}$ is H, C_{1-6}alkyl (optionally substituted with one or more of hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^9, R^9C_{1-6}alkylsulphanyl, R^9C_{1-6}alkylsulphinyl and R^9C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more of C_{2-6}alkenyl, C_{2-6}alkynyl, R^9, R^9C_{2-6}alkenyl, R^9C_{2-6}alkynyl, Het and trifluoromethyl), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^9-, R^9S-, R^9C_{1-6}alkylsulphanyl, *N*-(R^9C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino,

C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; **R^9** is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; **R^5** is H or C_{1-6}alkyl; and, **Het** is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; provided that: when R^1, R^2, R^3, R^4 and R^5 are all hydrogen, and X is NH, then Ar is not phenyl monosubstituted with CO_2H; and that when R^2, R^3, R^4 and R^5 are all hydrogen, R^1 is methyl, and X is NH, then Ar is not 4-(CO_2H)-phenyl; or a pharmaceutically acceptable salt thereof; for use as a medicament.

10. The use of a compound of formula (I):



(I)

wherein **Ar** is optionally substituted phenyl, optionally substituted naphthyl, Het, C_{3-12} cycloalkyl, or an optionally substituted 5 or 6 membered heteroaryl ring, said optional substituents being chosen from one or more of halo, C_{1-6}alkoxy, C_{1-6}alkyl, nitro, C_{1-6}alkanoylamino, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, aminoC_{1-6}alkyl, *N*-(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{1-6}alkyl, R^6S-, R^6C(O)- and R^6CH_2-; **R^6** is phenyl which is optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino,

C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; with the proviso that when Ar is a nitrogen linked Het, X is not –N(R^7)- or –O-; **X** is -N(R^7)-, -S(O)$_n$-, -O- or -SO_2N(R^7)-; **n** is 0, 1 or 2; $\mathbf{R^7}$ is H, C_{1-6}alkyl (optionally substituted with one or more of cyano, Het and R^{10}), C_{2-6}alkenyl (optionally substituted with R^{10}) or formyl; $\mathbf{R^{10}}$ is an optionally substituted five or six membered heteroaryl ring, optionally substituted phenyl or optionally substituted naphthyl said optionally substituents being chosen from one or more of halo, nitro, trifluoromethyl, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkoxy; $\mathbf{R^1}$ is H, C_{1-6}alkyl (optionally substituted with R^8), C1-6 alkylsulphanyl (optionally substituted with R^8), C_{2-6}alkenyl, R^8 or R^8S-; $\mathbf{R^8}$ is phenyl, C_{3-12} cycloalkyl, Het or a 5- or 6- membered heteroaryl ring, all of which are optionally substituted by one or more groups chosen from C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and benzyloxy, with the proviso that if R^1 is C_{1-6} alkylsulphanyl (optionally substituted with R^8) or R^8S- then X is –SO_2N(R^7)-; $\mathbf{R^2}$ is H or C_{1-6}alkyl; $\mathbf{R^3}$ is H or C_{1-6}alkyl; $\mathbf{R^4}$ is H, C_{1-6}alkyl (optionally substituted with one or more of hydroxy, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, R^9, R^9C_{1-6}alkylsulphanyl, R^9C_{1-6}alkylsulphinyl and R^9C_{1-6}alkylsulphonyl), C_{1-6}alkoxy (optionally substituted with one or more of C_{2-6}alkenyl, C_{2-6}alkynyl, R^9, R^9C_{2-6}alkenyl, R^9C_{2-6}alkynyl, Het and trifluoromethyl), C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, R^9-, R^9S-, R^9C_{1-6}alkylsulphanyl, *N*-(R^9C_{1-6}alkyl)carbamoyl, *N*-(HetC_{1-6}alkyl)carbamoyl, C_{1-6}alkanoylamino,

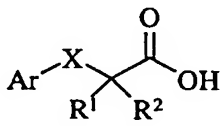
C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl; R^9 is optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring said optional substituents being chosen from one or more of C_{1-6}alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, mercapto, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; R^5 is H or C_{1-6}alkyl; and, **Het** is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal.

11. The use of a compound of formula (I) as defined in claim 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal.

12. A method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I) as defined in claim 10, or a pharmaceutically acceptable salt thereof.

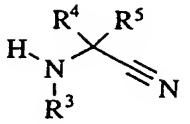
13. A process for preparing a compound of formula (I) as claimed in claim 1, the process comprising:

a) reacting an acid of formula **(II)**:



(II)

or a reactive derivative thereof, with an amine of formula **(III)**:



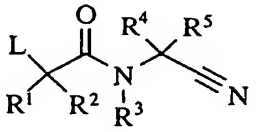
(III)

b) reacting a compound of formula **(IV)**:

Ar-X-H

(IV)

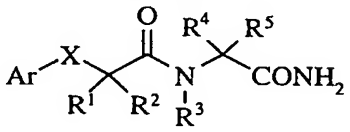
with a compound of formula **(V)**:



(V)

wherein L is a displaceable group;

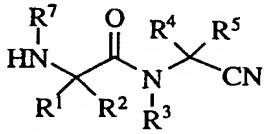
c) dehydrating a compound of formula **(VI)**:



(VI)

under standard conditions;

d) for compounds of formula **(I)** where X is $-SO_2N(R^7)-$, reacting a compound of formula **(VII)**:



(VII)

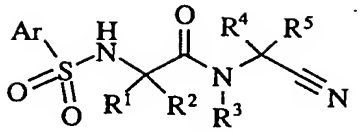
with a compound of formula **(VIII)**:

$Ar-SO_2-L$

(VIII)

where L is a displaceable group; or,

e) for the preparation of a compound of formula **(I)** where X is $-SO_2N(R^7)-$, reacting a compound of formula **(IX)**:



(IX)

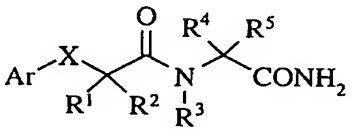
with a compound of formula (X):

R^7-L

(X)

wherein L is a suitable displaceable group.

14. Intermediate of formula (VI):



wherein R^1, R^2, R^3, R^4, R^5, X and Ar are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 00/00532

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D307/54 A61K31/335 A61K31/38 A61K31/275 C07D213/57
C07D333/24 C07D409/12 C07C255/29 C07D231/18 C07D513/04
C07D409/04 C07D233/84 A61P3/14 //(C07D513/04,277:00,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	example 1; table IX examples 8-10; table V examples 6-8; table VI examples 3,4; table VII	14
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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2000	16/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

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INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 00/00532

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

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Inter onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Inter nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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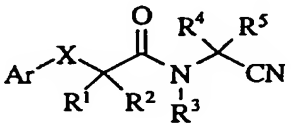
(54) Title: ACETAMIDO ACETONITRILE DERIVATIVES AS INHIBITORS OF CATHEPSIN L AND/OR CATHEPSIN S



(I)

(57) Abstract: A compound of formula (I) wherein Ar, R^1, R^2, R^3, R^4 and R^5 are defined; a composition comprising a compound of formula (I) and a carrier or diluent; a compound of formula (I) for use as a medicament, the use of a compound of formula (I) in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warn blooded animal; the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal; and a method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I).

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